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Technical Report

CRDLR 3015

VX
Percutaneous Studies in Man (U)

by

V. M. Sim, M.D.
Jane L. Stubbs

August 1960

ARMY CHEMICAL CENTER, MD.

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PERCUTANEOUS STUDIES IN MAN (U)

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Clincial Research Division

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(U)

FOREWORD

The work described in this report was authorized under Project 4C08-02-022, Medical Aspects of CW (U), Task 4C08-02-022-03, Clinical Investigation & Treatment of CW Casualties (U). The work was started in August 1959 and completed in April 1960.

Acknowledgments

In order to carefully evaluate and at the same time minimize the hazards inherent in such experimental studies, a comprehensive plan and a well-integrated, medical-biological experimental team were essential. The authors wish to express their gratitude to the following, without whose unselfish devotion this study could not have been completed: Miss Carol Lancaster, Clinical Research Division, assisted in more than 3000 individual red blood cell and plasma cholinesterase determinations. The staff of Basic Toxicology Branch, these Laboratories, completed a total of over 1000 individual whole-blood determinations, in addition to performing animal bioassay, agent administration, and spread measurements. Those who participated were Pfc. William Hickman, Sp/4 Albert Wade, and Pvts Ronald Biskup and John Murphy; Mrs. Willie Mae Lawson, Messrs. Leo Feinsilver, Charles V. Lisle, John London, and Myron Mehlman. Mr. Kenneth Wilson was responsible for the instrumentation and measurement of skin resistance. Dr. Elmer A. Lee and Captains Bernard Clark, Alvin Goodman, and Glenn D. Lubash were the medical officers participating. Miss Dorothy Ward and her staff, Technical Information Center, these Laboratories, searched for background references for this report. Dr. John Atkinson and staff prepared the statistical evaluation of the data.

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(C) DIGEST

(U) The effect of percutaneous administration of VX on 103 subjects using 50, 100, 200 μ aerosol particles, single and multiple drops, was studied. VX as neat agent, in doses from 5 to 35 μg/kg, was applied to the skin of right volar forearm, or hand, or neck.

(C) VX combined in a 1:1 mixture with each of three amines (n-octylamine, n-decylamine, or n-dodecylamine) was used with total VX doses of 10 to 20 μg/kg.

(C) It was found that both neat agent and agent-amine mixtures decreased the electrical resistance of the skin. One-to-one mixtures of n-octylamine or n-decylamine with 20 μg/kg of VX were about as effective as 35 μg/kg of neat agent.

(C) Twenty-five of 68 subjects who received either neat agent in doses of 20 to 35 μg/kg or amine-agent mixtures containing doses of 20 μg/kg of VX developed clinical signs and symptoms of anticholinesterase poisoning.

(U) The results from this study are of preliminary nature, therefore, conclusions cannot be drawn at this time.

(U) CONTENTS

(C) VX
PERCUTANEOUS STUDIES IN MAN (U)

I. (U) INTRODUCTION.

Previous studies of the penetration of anticholinesterases (antiChE) through human skin, either excised or intact, primarily concerned their rate of penetration. Various techniques, using radioactive-labeled compounds or neat agent, have been described. A review of both liquid and vapor studies was conducted in the United Kingdom, Canada, and the United States.

Work has been continuing in all three countries on various aspects of the problem of skin penetration. Rate of absorption and desorption, degree and rate of decomposition, evaporation as related to time, surface spread, physical constants relative to skin structure, and vapor and liquid interface systems have been determined.

All of the previous work[1,2] had a direct influence on the studies conducted in this paper. It was felt that previous studies would not answer the necessary questions for application of experimental work to field use and, therefore, more realistic dose levels had to be considered. In order to accomplish this with any degree of safety, some objective measure of biological effect would have to be utilized. The most reliable index in man, thus far, has been the level of cholinesterase (ChE) present in the blood.

Initial studies were made to determine the relationship of dose to the fall of ChE and appearance of signs and symptoms following intravenous administration of this compound. A subject was given a fraction of an estimated safe dose of VX rapidly over a 30-sec period. After 4 hr, allowing for changes in ChE levels, the dose was doubled (from 0.04 to 0.08 μg/kg; total dose was approximately 12 μg), and the experiment was repeated. This produced no significant drop in ChE and only minor subjective symptomatology.

Six months later, the same subject was given approximately 25 μg by rapid intravenous injection. This was followed by a continuous infusion of the agent at the rate of 1 μg/min over a 3-1/2-hr period until a total dose of 2.19 μg/kg had been administered. The experiment was terminated because of the condition of the subject. From this study,[3] it was estimated that the ChE50 for man would be approximately 1 μg/kg.

Another group of experiments was conducted to ascertain the validity of this calculation. The only variation was the duration of the infusion. It was found that 1 μg/kg intravenously administered produced a ChE50 in man. Administration of the agent over a shorter period of time altered the rate of ChE drop, but at this level it did not significantly alter the effect of the total dose after 12 or 24 hr.

On the basis of these preliminary studies, and being cognizant of recent studies both in Canada and the United Kingdom, experiments were designed to consider the following problems prior to experimentation on percutaneous penetration:

Which area of the skin is most suitable for study?

What is the most practical experimental method of application of agent?

What amount of agent is necessary to produce a ChE50?

What are the effects of agent-amine mixtures?

What is the practical significance of red blood cell (RBC), plasma, and whole-blood ChE values?

Is there a possible correlation between body weight and dose effect?

Is there a correlation between rate of fall and level of circulating ChE upon the incidence of signs and symptoms of intoxication?

Is spread of agent or agent-amine mixtures on the skin an important fact to be considered?

Is there evidence to alter our present concepts on the use of VX?

II. (C) METHODS AND PROCEDURES.

(U) Subjects were servicemen between the ages of 18 and 42 yr, with an average age of 24 yr. Each subject received a complete history and physical examination, blood and urine studies, electrocardiogram, chest X ray, psychological and psychometric tests, a psychiatric interview, and complete medical evaluation. Of 205 men examined, 103 comprised the test group. The maximum number on any test day was eight subjects.

A. (C) Physiological Observations and Measurements.

(U) The physiological observations and measurements before and during test periods of 24-hr duration included blood pressure, pulse and respiratory rates, chest and abdominal auscultations, measurement of skin resistance, grip strength by dynamometer, and measurement of area spread at 1, 10, 30, 60, 180, and 360 min after application of the material. In addition, signs and symptoms were recorded as they occurred.

(U) Clinical laboratory examinations were carried on in two separate laboratories simultaneously on aliquot portions of the same venous blood sample. Red blood cell and plasma ChE values were obtained 4 days prior to the test, usually during the week preceding, and on the morning of the test, by the modified ΔpH method of Michel as reported by Stubbs and Fales.[4] Whole-blood ChE levels were measured by the constant pH electrolytic method,[5] prior to experimentation and at 2-hr intervals following application.

(C) Bioassays (enzymatic and animal) were performed on each sample prior to the test. The potency of all samples in this work was between 90% and 95%. The biological activity of the amine-VX mixture was not examined prior to utilization, but the mixtures were prepared the morning of the test, using previously assayed agent.

B. (C) Choice of Skin Area and Means of Application.

Preliminary studies of 50-, 100-, and 150-μ aerosol particles, and single and multiple drops of neat agent, on various skin surfaces, such as the back of the neck, dorsum of hand and fingers, and the volar surface of the forearm, led to the selection of single-drop applications by means of an Agla micrometer syringe on the volar surface of the forearm for the following reasons:

1. It was the most practical available area on which definite decontamination, tourniquet, or excision could be performed, if required.

2. It confined the area necessary for such procedures to a minimum.

3. The aerosol dose required for reduction of circulating ChE was larger than that of single drops.

The additives were considered on the following bases:

1. The work performed in the United Kingdom had favored n-decylamine as the most promising on the basis of in vitro experimentation. Previous work in the United States on various species of animals favored either n-octylamine, n-decylamine, or n-dodecylamine in the primary series, and di-n-hexylamine in the secondary series.[6,7]

2. The highest practicable amine-agent ratio (equal parts) was chosen arbitrarily. Higher concentrations of amine-to-agent, as well as the more desirable lower ratios, have been tested in animals.[8,9]

Fifty-one subjects were utilized using 1:1 mixtures of n-octylamine, n-decylamine, n-dodecylamine, or di-n-hexylamine, and agent, with 1% Hiltamine* (amino dye) added for ultraviolet visualization of the drop area.

C. (U) Dose.

On the basis of previous work in animals and the intravenous infusion studies in man, initial estimates indicated that a 5-to-1 ratio between percutaneous and intravenous routes, respectively, would be a safe starting level. On the basis of the United States studies previously mentioned, the intravenous ChE50 appeared to be approximately 1 μg/kg. Accordingly, percutaneous experiments started at 5 μg/kg. In subsequent exposures, the dose was raised by increments of 5 μg/kg until biological effects and/or signs and symptoms appeared.

All experiments were conducted over a 24-hr period, with a 48- and 72-hr observation time. They were started between 0800 and 1000 hr, under ambient conditions of temperature and humidity (between 70° and 80°F and 40% and 70% RH). The skin surface of all subjects was examined carefully prior to application of agent. (The subjects were cautioned to avoid touching the contaminated region.) Subjects were allowed to be up and around the ward when not undergoing those physiological measurements that required bed rest. No attempt was made to control food or water intake and smoking was allowed.

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* A Parke, Davis & Company product.

D. (U) Measurement of Skin Resistance.

The Wheelan skin-resistance meter[10] was used in all experiments at an indicated current of 2 μa. Two types of electrodes were utilized: the standard zinc/zinc sulfate electrodes filled with an agar-gel-ZnS04 electrolyte and the silver disc electrodes 1/2 in. in diameter, coated with a gum of 2% cellosize containing one half saturated KCl solution. The latter electrodes were found to be the most satisfactory. In conducting the measurement procedures, one electrode was placed over a puncture in the skin (venipuncture) and the other over the area to be tested. During the later phases of this work a vibrating reversing switch was added to the circuit between the skin electrodes and the meter, followed by substitution of a standard decade resistance box adjusted to give the same indicated current on the skin meter. The value of skin resistance was then read off the box. With this added feature, reasonably satisfactory results were obtained.

III. (C) RESULTS.*

A. (U) Neat Agent.

Forty subjects were given 5 to 35 μg/kg of single drop, neat agent, the larger part of the group receiving the higher doses. Twelve subjects were given 20 μg/kg of multiple doses, neat agent. Table 1 shows that the intravenous administration of 1 μg/kg produced an average fall of whole-blood ChE to 43% of normal (range 38% to 46%). Table 2 indicates that the percutaneous administration of 35 μg/kg produced an average fall of whole-blood ChE to 44% of normal (range 9% to 77%, see table 1, appendix). This wide range of variability in the percutaneous values contrasts with the narrow range of the intravenous values. With the information on the intravenous dose and the resultant ChE level as a baseline, examination of the percutaneous data seemed to indicate a linear relationship between the amount of agent applied to the amount absorbed. However, the variability in individual exposures at the same dose level was high. Nevertheless, the data seemed to indicate a percutaneous-to-intravenous ratio of effectiveness of 1 to 33.

* (U) All the detailed experimental data are tabulated and contained in the appendix of this report.

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TABLE 1

(U) INHIBITION OF HUMAN WHOLE-BLOOD ChE AS RELATED TO INTRAVENOUS DOSE OF NEAT VX

Dose*	ChE	
	Average	Range
μg/kg	% of normal	
0.25	76	(70-88)
0.50	67	(56-69)
0.75	60	(50-64)
1.00	43	(38-46)

* VX administered to six subjects. Infusion time varied from 105 to 240 min.

(U) TABLE 2

INHIBITION OF HUMAN WHOLE-BLOOD ChE AS RELATED TO PERCUTANEOUS DOSE OF NEAT VX

Dose	Number of subjects	Average time for minimal ChE	Average minimal ChE	Maximum dose absorbed*	Applied dose absorbed*
μg/kg		hr	% of normal	μg/kg	%
5	7	4	96	0.04	0.8
10	2	6	89	0.11	1.1
15	2	5	82	0.19	1.3
20	5	8	72	0.36	1.8
25	10	10	66	0.54	2.1
30	6	10	63	0.68	2.3
35	8	10	44	0.94	2.7

* Based on the intravenous infusion of VX in six subjects.

Note: This table shows the mean whole-blood ChE for a dose level at a specified time. The data here do not correspond with the detailed data given in table 1, appendix, because only the whole-blood ChE was determined during one period of the program. The same subjects used during this particular phase are included in this table but not in table 3.

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B. (C) Agent-Amine Mixtures.

Fifty-one subjects were studied in the 10 to 20 μg/kg agent-amine mixture groups, utilizing the exact procedures as with neat agent, but using 1:1 mixtures of VX with n-octylamine, n-decylamine, n-dodecylamine, or di-n-hexylamine. Table 3 indicates a depression of whole blood as related to percutaneous dose of VX with n-octylamine. At a dosage of 20 μg/kg, the average whole-blood ChE is 21% of normal (range 9% to 43%); see also table 2, appendix. The average RBC ChE in this 20 μg/kg group dropped to 26% of normal (range 11% to 48%). Insufficient whole-blood determinations were made for the other two amine-agent mixtures. The mean decline in RBC-ChE values for 20 μg/kg n-decylamine was to 34% of normal (range 17% to 53%) and for n-dodecylamine to 58% of normal (range 32% to 97%).

(C)

TABLE 3

INHIBITION OF HUMAN WHOLE-BLOOD ChE AS RELATED TO PERCUTANEOUS DOSE OF VX WITH N-OCTYLAMINE MIXTURE (1:1) (C)

Dose	Number of subjects	Average time for minimal ChE	Average minimal ChE	Maximum dose absorbed*	Applied dose absorbed*
μg/kg		hr	% of normal	μg/kg	%
5	1	10	85	0.15	3.0
10	1	10	84	0.45	4.5
15	3	7	91	0.84	5.6
20	8	11	21	1.20	6.0

* Based on intravenous infusion of VX in six subjects.

Note: This table shows the mean of the minimal values at each dose level for each group of subjects as shown in the appendix.

C. (C) Minimal Values of ChE.

(U) The figures shown in tables 4 and 5 are average minimal ChE values which occurred within the first 12 hr (table 4) and within 24 hr (table 5) after application of the neat agent or agent-amine mixtures. All data from 20 to 35 μg/kg of the neat-agent group and all data at 20 μg/kg of the mixtures are included. In addition, a comparison was made at 20 μg/kg of neat agent as a single drop as compared with the same total dose applied in five discrete drops on the same surface area of the forearm. Care was taken to place the drops far enough apart to prevent confluence by spreading after application.

(C)

TABLE 4

AVERAGE MINIMAL VALUE OF ChE WITHIN 12 HR OF APPLICATION OF AGENT NEAT OR AGENT-AMINE MIXTURES (C)

Agent	Diameter of droplet	Dose	RBC	Plasma	Whole blood
	mm	μg/kg	% of normal		
	Single drop				
Neat VX	1.388	20	65	80	61
	1.495	25	65	60	53
	1.589	30	76	77	70
	1.673	35	32	59	41
	Multiple drops				
	0.812	20	60	78	-
	Single drop				
VX - n-octylamine (1:1)	1.819	20	27	57	21
VX - n-decylamine (1:1)	1.817	20	36	57	36
VX - n-dodecylamine (1:1)	1.811	20	58	77	46
Least significant difference			13.5	19.2	26.9

(C) TABLE 5

AVERAGE MINIMAL VALUE OF ChE WITHIN 24 HR OF APPLICATION OF AGENT NEAT OR AGENT-AMINE MIXTURES (C)

Agent	Dose	RBC	Plasma	Whole blood
	µg/kg	% of normal		
	Single drop			
Neat VX	20	59	97	73
	25	60	78	55
	30	68	117	76
	35	28	67	43
	Multiple drops			
	20	57	105	-
	Single drop			
VX - n-octylamine (1:1)	20	45	80	30
VX - n-decylamine (1:1)	20	39	67	34
VX - n-dodecylamine (1:1)	20	47	88	43
Least Significant Difference		23.6	22.4	26.3

(U) Differences of statistical significance ($P < 0.05$) were found between dosage levels of 20 and 35 µg/kg in respect to RBC, plasma, and whole-blood ChE values.

D. (U) Predicted ChE50.

Using the method of Bliss,[1] the dose-response curves were computed for varying levels of neat agent using 12- and 24-hr values for RBC, plasma, and whole blood, as shown in tables 4 and 5.

PREDICTED AMOUNTS OF NEAT VX REQUIRED FOR ChE50 (U)

Time period	RBC	Plasma	Whole blood
hr		μg/kg	
12	34	54	36
24	29	52	37

E. (C) Relationship of Body Weight and Spread of Agent on Skin Surface.

The relationship of the body weight of the volunteers and the spread of the agent on resulting ChE levels was investigated. This was done by fitting multiple or single regressions of ChE levels as Y, body weight as X_1, and spread as X_2. If the regression coefficients were found to be significant, then information regarding ChE was obtained by knowing the body weight and/or the spread of the agent.

Nine multiple regressions were examined and in only one of these was a significant prediction found. In the n-octylamine group, where both weight and spread were known, both factors gave information. The prediction formula in this group was ChE = 39.52 - 0.31 kg + 11.62 spread. In this instance, the predicted ChE was less with large than with small men and greater with large-spread measurements.

The other eight groups investigated and found not to predict ChE are as follows:

Neat VX, single drop, 20 μg/kg - Spread only
Neat VX, single drop, 20 μg/kg - Weight only
Neat VX, single drop, 20 μg/kg - Weight and spread
Neat VX, single drop, 35 μg/kg - Weight and spread
Neat VX, multiple drops, 20 μg/kg - Weight and spread
n-Decylamine-VX, 20 μg/kg - Weight only
n-Decylamine-VX, 20 μg/kg - Weight and spread
n-Dodecylamine-VX, 20 μg/kg - Weight and spread

F. (C) Skin Resistance.

Control measurements were made before application of agent of the 24 subjects used in the skin resistance test and each subject was examined 10 and 30 min and 1, 3, and 6 hr after application of agent. Additional readings after 24 hr were made in two cases in order to follow the spread of neat VX. The least change of resistance was found in those cases where the additive-VX mixture was used and the greatest change in subjects when neat VX was applied. The ratio of final-to-initial resistance was between 2 to 3 and 1 to 4, with absolute values under 0.5 megohms initially.

At 4 hr, the electrical plot so obtained was identical with the area visualized by Hiltamine stain. At 24 hr, the area of spread found electrically was two to three times greater than that found at 4 hr, whereas the weak Hiltamine stain remaining at 24 hr covered about the same area as that found at 4 hr. Further, the applications of mixtures not only produced frank skin damage, but both the dye and the electrical plot indicated alteration under the point of application. The evidence presented must be considered qualitative rather than quantitative, but it definitely indicates a much lowered skin resistance after application of either neat VX or VX-additive mixtures.

G. (C) Comparison of Average Drop in ChE after 12 and 24 hr.

Comparison of the 12- and 24-hr values in each group of all three ChE determinations, utilizing the method of least significant differences, gave the following information (table 6):

(C) TABLE 6

RELATION OF 24-HR ChE TO 12-HR ChE ACCORDING TO AGENT AND BLOOD COMPONENT (U)

Agent	Dose	Blood component*		
		RBC	Plasma	Whole blood
	μg/kg			
Neat VX, single drop	20	0	0	0
	25	0	0	0
	30	0	+	0
	35	0	0	0
Neat VX, multiple drops	20	0	+	0
n-Octylamine-VX, 1:1 mixture	20	+	+	0
n-Decylamine-VX, 1:1 mixture	20	0	0	0
n-Dodecylamine-VX, 1:1 mixture	20	0	0	0

* 0 = No significant difference.
+ = 24 hr significantly greater than at 12 hr.
- = 24 hr significantly less than at 12 hr.

The importance of these observations is not known. Since whole-blood values are a reflection of both plasma and RBC, it would seem possible that at lower dose levels of both the single and multiple drops of neat agent, the results noted were a reflection of rather marked plasma changes upward. This was seen particularly at the lower dose levels. Results might also be interpreted to mean that the addition of amines, particularly n-octylamine seemed to facilitate the absorption of the material through the skin more rapidly, but had comparative total-dose effects when 24-hr absorption was considered. Comparison of single-drop and multiple-drop figures confirmed an early impression that the rise in plasma levels occurred consistently between 12 and 24 hr, whereas the RBC levels usually were at the same level except for n-octylamine which was significantly greater.

H. (C) Signs and Symptoms as Related to ChE Depression; Dose-Effect Relationship.

(U) Of 42 subjects receiving doses of neat agent from 20 to 35 μg/kg, 9 became ill within the first 12 hr after administration of the agent. Four of these occurred at 35 μg/kg, three at 20 μg/kg, and two at 25 μg/kg doses. The average depression of the RBC ChE for the 9 ill subjects for 12 and 24 hr was to 30% and 31% of normal, and for the 24-hr whole blood was to 43% of normal.

(C) Of 26 subjects receiving μg/kg VX-amine mixtures, 16 became ill. Eight of these subjects were in the n-octylamine group and four each in the n-decylamine and n-dodecylamine groups. Average 12-hr RBC figures dropped to 25% of normal for n-octylamine and n-decylamine groups, but to 47% of normal for the four subjects who became ill in the n-dodecylamine group; the 24-hr figures for RBC dropped to 46%, 30%, and 32% of normal, respectively, and in a like manner, the 24-hr whole-blood values were 30%, 29%, and 34% of normal, respectively.

I. (C) Relationship of Spread to Incidence of Intoxication.

Records of 58 subjects were examined for possible relationship of increased or lack of spread as being a possible factor in intoxication. Differences between the 1- and 3-hr measurements were converted to square centimeters of area and expressed as a plus value if the 3-hr figure was greater, and as a negative value if less (see appendix tables). The average spread was then compared with the number in the group who had definite signs and symptoms of intoxication associated with significant ChE depression. As may be seen from table 7, the groups demonstrating the least degree of change in spread produced the greatest effect.

(C) TABLE 7

RELATIONSHIP OF SPREAD TO INCIDENCE OF INTOXICATION (U)

Agent	Dose	Number of subjects ill	Average increase from 1 to 3 hr
	μg/kg		sq cm
Single drop			
Neat VX	20	2/10	3.7
	25	2/7	11.5
	30	0/5	7.9
	35	4/8	3.8
Multiple drops			
	20	1/12	4.6
Single drop			
VX - n-octylamine (1:1)	20	8/8	0.7
VX - n-decylamine (1:1)	20	4/10	2.5
VX - n-dodecylamine (1:1)	20	4/8	2.7

J. (U) Signs and Symptoms of Anticholinesterase Poisoning.

Onset of symptoms rarely occurred prior to 6 hr. It was not always possible to assess or note the exact time of onset of symptoms, but they usually occurred in the approximate following order: Local sweating at the site of application was often noted first; muscular fasciculation was infrequently reported and was actually seen only in two subjects; usually the subjects preferred to rest quietly in bed and complained of little except being tired; a feeling of weakness; increase in abdominal distension; slight nausea or lack of appetite; occasionally subjects complained of vague headaches, which were usually associated with a feeling of lassitude and a lack of desire to either participate in card games or other activities.

It was observed that the more rapid the fall in the ChE, the shorter the time from application of material to symptoms in subjects. Severe nausea and vomiting, when it occurred, were often of several hours duration. Weakness in the more severely intoxicated group was present in some instances as long as 72 hr.

Blood pressure and pulse and respiratory rates were usually unaffected except during and after the paroxysms of vomiting. Hand dynamometer readings were done on occasional subjects, but were thought to be too crude a measurement to be reliable. The incidence of respiratory symptoms and pupillary constriction was <5%.

In a review of all subject records the symptoms produced, as related to RBC-ChE levels, might be classified in the following manner:

Levels below 50% of normal.

Headaches which were rarely associated with measurable pupillary constriction

From 40% to 30% of normal.

Slight nausea and headache were common

From 30% to 20% of normal.

The nausea became more severe; abdominal cramps were often present and vomiting occurred; weakness; photophobia; a feeling of "chilliness" was often described

From 20% to 10% of normal.

The nausea, vomiting, abdominal cramps, and weakness became more severe and protracted; pupillary constriction and diarrhea were also present in a few subjects.

K. (U) Calculation of Rate of Penetration of Neat Agent.

The rate of penetration of neat agent in all eight subjects in the 35 μg/kg group was determined by measuring the time from application of the agent to the time when the first significant drop in RBC-ChE (15%) occurred. From this biological measurement it was calculated that the

average time delay was 3.4 hr. Taking the average of the total square-centimeter measurements at the end of 3 hr, and considering the spread to be a rectangle, the average surface area was 18.4 sq cm. Taking the absolute amount of agent applied by means of weight times dose, the average weight being 70.5 kg, the mean absolute dose is 2.5 mg/man.

Assuming that the major portion of the agent had penetrated by the time required to produce a maximum depression of RBC-ChE, an average mean time to produce this maximum fall was found to be 11 hr (660 min).

Subtracting the delay time, 204 min (3.4 hr), from the time to average maximum depression (660 min) resulted in an absorption period of 456 min.

Therefore,

$$X = \frac{2.5 \times 10^3}{18.4 \times 456} = 0.3\ \mu g/\text{sq cm/min}$$

This calculation is actually open at both ends, particularly in the amount required to produce an observable biological effect. This, plus the additional amount of agent which can be assumed to be absorbed after the 11-hr period, would necessarily raise the above figure of absorption rate. Irrespective of this, the calculation might be more correct if the surface area were considered elliptical ($1/2D \times 1/2D \times \pi = 1/4\ \pi D^2$), in which instance the rate would be 0.37 μg/sq cm/min. In addition, according to our data, the amount of agent required to be absorbed in order to produce this 15% depression is approximately 0.11 to 0.13 μ.

IV. (C) DISCUSSION.

(U) Prior to discussion of the experimental findings, certain conditions of the study should be reviewed briefly. The majority of the tests utilized single-droplet administrations on the relatively hairless volar surface of the forearm. There was no preliminary pretreatment nor washing of the skin surface before application. No attempt was made to prevent evaporation of the agent from the skin surface nor were any decontamination procedures carried out.

(U) There appeared to be a practical difference between RBC and plasma as compared with whole-blood values, particularly at lower dosage levels. The plasma values seemed to show the first indication of depression, followed by the RBC. Usually the whole blood did not start to drop at these lower doses until there was at least a 15% drop in RBC. At dosage levels from 20 μg/kg and up, the correlation between the two methods was much

better. In most instances, the 12- and 24-hr RBC levels were the lowest, the plasma values usually rose after the 12-hr period, and the whole-blood values were usually slightly higher than RBC, reflecting the plasma increase after the first 12 hr. The recovery of all values in the first 48 hr indicated that the return toward a normal ChE level was more rapid than had previously been noted in studies of the percutaneous application of GB and GA. This difference suggests several possibly reasons. There are both physical and chemical differences in the agents, and it would seem logical that there are chemical and possibly physical differences after being in contact with the skin for varying periods of time.

(C) Rate of fall of ChE levels was examined with reference to time of onset and incidence of signs and symptoms. Those subjects who had drops in ChE over 50% in the first 6 hr usually seemed to develop signs and symptoms of intoxication. This was particularly true in the n-octylamine-VX and n-decylamine-VX groups at 20 μg/kg, and those subjects receiving higher doses of neat agent. There were exceptions demonstrating the extreme variability from subject to subject.

(C) Examination of the surface spread of the agent by ultraviolet visualization of Hiltamine was of value, but measurement of electrical resistance revealed that the neat agent tended to spread two to three times more over the 24-hr period than could be visualized by Hiltamine. Both the neat agent and agent-amine mixtures reduced the electrical resistance of the skin. However, the agent-amine mixtures appeared to stay more circumscribed and the spread was minimal after 3 hr. This localization of larger amounts of agent over a smaller area seemed to reduce the penetration time required for biological effect as demonstrated by the drop in ChE. Early appearance of mild erythema at site of application occurred most frequently in the n-octylamine-VX and n-decylamine-VX groups, but did in some instances occur with neat agent as well. Local sweating was rarely observed, but many subjects noticed a cool sensation for as long as 72 hr at the site of application. Local fasciculation was observed only twice and it was minimal. This has been observed previously by both the United Kingdom and the United States investigators with GB, GA, and GD.

(C) One of the significant differences between application of neat agent or the agent-amine mixture was that it required less agent-amine to produce a definite and predictable fall in ChE. In addition, it will be noted that this was not significant in the 12- and 24-hr values (table 4 and 5). However, agent-amine subjects often manifested more rapid depressions in ChE in the first 12 hr that were associated with toxic signs and symptoms.

This observation would suggest that at any given dose employed, the amine delivered more agent to the blood stream per unit of time. An equally significant observation in this respect was the evidence that whereas there were very wide differences in response to a given dose of neat compound, the amines, especially n-octylamine and n-decylamine, seemed to give a predictable fall with much less variability. For these reasons alone, the problem of additives is worthy of serious consideration from the biological standpoint. There are many other compounds that might be equally or more effective than amines, but final decision would have to depend on manufacture, stability, and other physical and chemical characteristics. There is no doubt now that such studies should be completed before feasibility studies are continued.

(C) Specifically, it must be determined which of the many additives that have been under study are compatible with the agent under all conditions of munitions manufacture, storage, and expenditure. Secondly, consideration must be given to certain compounds, such as phosgene oxime and other compounds, which are known to cause skin damage. Would early awareness of pain be balanced by the speed of penetration of the lethal agent with compounds like phosgene oxime, capsicum, or others? Mustard might possibly be considered favorably, but it might also be objectionable for other reasons, particularly the detection by odor.

(C) The percutaneous LD50 for man can be estimated provided the limitations of these experiments are realized. The environmental conditions were those of a temperate climate. The skin area used was in most instances a relatively hairless surface, and completely free of any identifiable injury. After a great deal of work in the United Kingdom, Canada, and the United States, there is reasonable agreement that an extrapolation factor of 4 for GB and 5 for GA is rational for ChE50:LD50. These calculations were based on all available data obtained in animals, primarily by the intravenous and respiratory routes, but were not necessarily considered wholly adequate for percutaneous studies because of the instability of the agents. Considerable evidence has been presented by all three countries that there is less reliability to this methodology in percutaneous VX studies. This is to be expected if one considers that the comparative anatomy of blood vessels and respiratory tracts of man and animals are more similar than their respective skins. Likewise, it seems logical that introduction of an agent either directly into the circulation or by inhalation would produce more comparable results than placing the agent on the varied skin surfaces under a variety of conditions of depilation, clipping, etc. However, there is agreement that both man and animals can tolerate considerable doses of antiChE if the rate of administration is very slow, as with a single dose, or is absorbed gradually over several

days by exposure to fractions of a lethal dose. These individuals usually have only minimal signs and symptoms when such exposures occur.

(U) However, evidence was presented several times that rapid administration of antiChE produced predictable drops in enzyme levels, and when the amount was sufficient to depress this level below 50% of normal, there was a rapid appearance of toxic signs and symptoms. There was further evidence that 1 μg/kg of VX given slowly, intravenously, over a 2- to 4-hr time period will produce a predictable 50% ChE inhibition. Furthermore, an additional 1 μg/kg given in the same experiment definitely caused the appearance of moderately severe toxic signs and the associated drop to about 10% of normal value. There was ample evidence in these studies indicating that there was a definite correlation between the level of circulating ChE and symtomatology, provided the absorption rate was such that the actual penetration period was 7 hr or less, allowing for 3.4-hr initial delay before biological effects were apparent.

(C) Another finding of interest resulted from clinical observation that subjects who had a considerable increase in visible spread of the agent within the first 3 hr did not become ill and had minimal ChE drops. Those who exhibited little increase in spread invariably had low ChE levels, which were always associated with toxic signs and symtomatology. This suggests that an optimum concentration of agent over a given area of skin is required to overcome area defense mechanisms, and that once this barrier, reservoir, resistance, or other biological defense systems are overcome, the problem becomes subject to the physical laws of liquids and can be predicted by mathematical formula. Ainsworth[1,2] was the first to predict by mathematical formula the rate of penetration of VX, and subsequently substantiated the theorem using labeled agent in excised skin perfusion studies. There is remarkable agreement between these present studies and those of Ainsworth, particularly in view of the difference in state of test tissues and methodology employed.

(C) On the basis of the foregoing discussion, it appears that there is enough evidence at hand to predict an LD50 for man under the conditions of this experiment, because of the evidence that the ChE50 for man is 1 μg/kg intravenously and approximately 32 μg/kg percutaneously. Utilizing the higher factor of 5 for extrapolation to LD50 for conservative reasons, allows a firm prediction of a 1-mg total dose by intravenous administration for the average 70-kg man. In like manner, the estimated LD50 for 1:1 n-octylamine-VX mixture is estimated to be 7-mg total dose and for neat agent, 10-mg total dose. These estimates are arrived at on the conservative side by utilizing the average dose required to produce an actual ChE level of 30% of normal or

below. There is no disagreement that at this level all subjects have symptoms which gradually increase in severity on further depression. It would seem unlikely that there would be disagreement that five times the dose required to produce symptoms, as seen in these experiments, would be a conservative LD50 estimation for man for an acute exposure.

V. (U) CONCLUSIONS.

The results from this study are of a preliminary nature; therefore conclusions can not be drawn at this time.

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(U) **UNCLASSIFIED**

APPEND

TABLE

EFFECT OF SINGLE DROP AND FIVE
(Right Volar

Subject	Race	Age	Weight	Spread			RBC					Initial	
				Early	Late	Maximum	Initial	Minimal*		At 24 hr			
			kg	sq cm			ΔpH		% initial	ΔpH	% initial	ΔpH	
5 μg/kg neat VX,													
1-59, R.W.B.	W	19	76	-	-	-	0.94	0.77 (4)	82	0.63	67	0.60	0.64
2-59, L.E.S.	W	24	64	-	-	-	0.76	0.81 (6)	107	0.76	100	0.68	0.72
4-59, T.E.D.	W	23	70	-	-	-	0.81	0.80 (4)	99	0.86	106	0.99	0.82
5-59, L.E.M.	W	20	72	-	-	-	0.88	0.86 (2)	98	0.90	102	0.61	0.52
6-59, R.A.LeT.	W	18	69	-	-	-	0.93	0.80 (4)	86	0.83	89	0.51	0.43
7-59, R.T.McQ.	W	20	78	-	-	-	0.82	0.73 (6)	89	0.84	102	0.66	0.67
10 μg/kg neat VX,													
8-59, R.A.C.	W	18	-	-	-	-	0.85	0.67 (11)	79	0.59	69	0.68	0.51
9-59, D.F.R.	W	24	-	-	-	-	0.90	0.74 (11)	82	0.82	91	0.61	0.42
15 μg/kg neat VX,													
10-59, R.D.S.	W	20	-	-	-	-	0.88	0.63 (8)	72	0.57	76	0.55	0.49
11-59, A.R.S.	N	26	-	-	-	-	0.97	0.74 (11)	76	0.61	63	0.60	0.48
20 μg/kg neat VX,													
1-60, A.D.S.	W	21	75	13.5	10.5	-3.0	0.73	0.21 (12)	29	0.21	29	0.65	0.58
2-60, D.M.H.	W	22	75	16.3	13.9	+2.4	0.72	0.27 (12)	38	0.26	36	0.68	0.56
3-60, D.R.T.	W	31	66	16.7	13.3	+3.4	0.75	0.58 (10)	77	0.50	67	0.78	0.62
4-60, R.F.B.	W	21	81	13.5	12.0	+1.5	0.67	0.59 (10)	88	0.54	80	0.81	0.72
6-60, J.H.H.	W	19	69	9.8	11.2	+1.4	0.79	0.59 (8)	75	0.50	63	0.67	0.49
19-59, J.P.B.	W	21	82	-	-	-	0.99	0.63 (11)	64	0.58	59	1.00	0.63
23-59, L.R.DeL.	W	21	80	-	-	-	0.91	0.39 (8)	43	0.23	25	0.81	0.74
27-59, D.W.	W	20	73	3.7	14.0	+8.68	0.86	0.62 (10)	72	-	-	-	0.52
33-59, G.H.M.	W	21	73	2.2	7.6	+5.4	0.80	0.70 (11)	88	0.74	92	0.51	0.39
34-59, H.E.K.	W	29	93	2.6	5.9	+3.3	0.90	0.65 (8)	72	0.70	78	0.70	0.44
20 μg/kg neat VX,													
29-60, T.A.F.	W	22	80	74.1	77.8	+3.7	0.77	0.50 (10)	65	0.51	66	0.74	0.10
30-60, E.R.R.	W	29	70	93.7	99.4	+5.7	0.80	0.57 (10)	71	0.32	40	0.77	0.60
31-60, J.F.S.	W	21	65	101.7	108.1	+6.4	0.86	0.55 (10)	64	0.39	45	0.67	0.51
32-60, C.J.S.	W	18	60	77.4	81.4	+4.0	0.61	0.11 (10)	18	0.13	21	0.73	0.41
33-60, E.P.B.	W	32	70	84.4	88.9	+4.5	0.84	0.32 (10)	38	0.44	52	0.76	0.67
35-60, E.J.K.	W	18	69	94.2	103.5	-9.3	0.83	0.60 (8)	72	0.51	61	0.66	0.53
36-60, G.F.F.	W	20	76	69.0	68.3	-0.7	0.77	0.20 (10)	26	0.21	27	0.74	0.65
25-60, A.D.DeP.	W	20	75	55.8	67.0	+11.2	0.75	0.66 (5)	88	0.73	97	0.80	0.76
26-60, L.E.K.	W	18	68	59.4	61.1	+1.7	0.78	0.61 (12)	78	0.60	77	0.69	0.64
27-60, F.R.L.	W	20	61	67.2	72.5	+5.3	0.79	0.40 (7)	50	0.43	54	0.53	0.52
28-60, A.B.M.	W	24	96	86.9	88.8	+1.9	0.89	0.74 (8)	83	0.74	86	0.90	0.80
34-60, C.H.C.	N	28	72	86.9	85.6	-1.3	0.76	0.51 (10)	67	0.41	54	0.69	0.58
25 μg/kg neat VX,													
45-59, T.L.A.	W	26	87	1.8	10.6	+8.8	0.82	0.70 (13)	85	0.62	76	0.82	0.42
46-59, S.A.M.	W	20	63	2.5	10.6	8.1	0.83	0.24 (11)	29	0.30	36	0.91	0.52
52-59, B.C.R.	W	19	65	2.7	14.8	12.1	-	- -	-	-	-	-	-
69-59, F.J.W.	W	21	79	3.8	16.0	12.2	0.69	0.63 (9)	91	0.49	71	0.62	0.27
70-59, F.R.L.	W	28	93	2.9	17.4	14.5	0.72	0.71 (9)	99	0.75	104	0.83	0.64
71-59, N.A.F.	W	24	75	3.2	16.2	13.0	0.66	0.35 (9)	53	0.31	47	0.72	0.48
72-59, D.D.	W	30	80	2.3	13.8	11.5	0.71	0.23 -	32	0.20	28	0.71	0.45
30 μg/kg neat VX,													
7-60, S.B.	N	30	74	11.1	11.6	0.5	0.61	0.44 (12)	72	0.36	58	0.73	0.61
8-60, J.S.	W	24	80	15.2	18.7	3.5	0.76	0.62 (10)	82	0.53	70	0.59	0.62
66-59, M.I.C.	W	21	57	3.6	14.0	10.4	0.73	0.56 (8)	77	0.40	55	0.61	0.37
67-59, L.E.B.	W	18	56	3.9	13.5	9.6	0.71	0.45 (8)	63	0.45	63	0.55	0.39
68-59, A.P.H.	W	21	78	3.2	18.9	15.7	0.68	0.60 (9)	88	0.63	93	0.69	0.44
35 μg/kg neat VX,													

APPENDIX

TABLE 1

DROP AND FIVE DROPS OF NEAT VX ON MAN (U)
(Right Volar Forearm)

Cholinesterase										Local and systemic signs and symptoms
Plasma					Whole blood					
Initial	Minimal*		At 24 hr		Initial	Minimal*		At 24 hr		
	ΔpH	% initial	ΔpH	% initial	μeq/ml min^{-1}		% initial	μeq/ml min^{-1}	% initial	
g/kg neat VX, single drop										
0.60	0.64 (11)	107	0.71	118	6.8	5.5 (8)	81	-	-	-
0.68	0.72 (6)	106	0.89	131	7.3	5.9 (7)	81	-	-	-
0.99	0.82 (2)	83	0.97	98	5.9	5.6 (1)	95	-	-	-
0.61	0.52 (2)	85	0.68	111	6.2	6.1 (5)	98	-	-	-
0.51	0.43 (4)	84	0.68	133	6.1	5.8 (11)	95	-	-	-
0.66	0.67 (10)	101	0.79	120	5.3	4.5 (9)	85	-	-	-
g/kg neat VX, single drop										
0.68	0.51 (11)	75	0.74	109	5.3	4.3 (6)	81	-	-	-
0.61	0.42 (2)	69	0.64	105	5.5	5.0 (1)	91	-	-	-
g/kg neat VX, single drop										
0.55	0.49 (11)	89	0.67	122	5.6	4.0 (4)	71	-	-	-
0.60	0.48 (11)	80	0.70	116	5.7	4.8 (2)	84	-	-	-
g/kg neat VX, single drop										
0.65	0.58 (10)	89	0.62	95	6.1	1.6 (12)	26	-	-	-
0.68	0.56 (10)	82	0.48	71	6.0	2.4 (10)	40	-	-	Nausea; bowel sounds
0.78	0.62 (10)	80	0.63	81	6.3	4.2 (6)	67	-	-	-
0.81	0.72 (10)	89	0.94	116	6.1	3.9 (6)	64	-	-	-
0.67	0.49 (2)	73	0.77	115	7.5	4.4 (6)	59	-	-	-
1.00	0.63 (11)	63	0.64	64	6.3	4.4 (8)	70	3.7	59	-
0.81	0.74 (7)	91	0.71	88	6.7	2.0 (5)	30	3.4	50	Erythema; nausea; fasciculation; pain
-	0.52 (5)	90	-	-	5.2	4.0 (10)	77		-	-
0.51	0.39 (5)	76	0.63	123	4.4	4.4 (5)	100	4.7	106	-
0.70	0.44 (4)	63	0.83	120	6.2	5.0 (10)	81	4.9	79	-
g/kg neat VX, five drops										
0.74	0.10 (10)	13	0.80	108	-	-	-	-	-	-
0.77	0.60 (10)	78	0.74	96	-	-	-	-	-	-
0.67	0.51 (10)	76	0.66	99	-	-	-	-	-	-
0.73	0.41 (10)	56	0.44	60	4.7	-	-	-	-	Nausea; vomiting; administered 2 mg of atropine
0.76	0.67 (10)	88	0.78	103	-	-	-	-	-	-
0.66	0.53 (10)	80	0.73	111	-	-	-	-	-	-
0.74	0.65 (8)	88	0.70	95	-	-	-	-	-	-
0.80	0.76 (5)	95	0.80	100	5.0	-	-	-	-	-
0.69	0.64 (2)	93	0.96	139	5.0	-	-	-	-	-
0.53	0.52 -	98	0.59	111	4.8	-	-	-	-	-
0.90	0.80 (8)	89	1.12	124	5.2	-	-	-	-	-
0.69	0.58 (10)	84	0.77	112		-	-	-	-	-
g/kg neat VX, single drop										
0.82	0.42 (8)	51	0.54	66	5.6	5.1 (5)	91	5.6	100	Fasciculation; nausea; vomiting; headache
0.91	0.52 (8)	57	0.50	55	5.6	1.4 (12)	25	1.6	28	-
-	- -	-	-	-	6.3	1.7 (11)	27	1.2	19	-
0.62	0.27 (8)	44	0.58	94	5.7	4.7 (9)	83	4.8	84	-
0.83	0.64 (2)	77	0.95	114	6.3	5.1 (8)	81	5.1	81	-
0.72	0.48 (9)	67	0.57	79	5.3	2.5 (8)	47	2.4	45	-
0.71	0.45 (6)	63	0.41	58	6.3	1.1 (8)	17	1.7	27	Headache; bowel sounds
g/kg neat VX, single drop										
0.73	0.61 (10)	84	0.80	110	6.3	4.0 (10)	63	-	-	-
0.59	0.62 (10)	105	0.79	134	7.3	5.8 (7)	79	-	-	-
0.61	0.37 (8)	61	0.53	87	5.0	3.5 (9)	70	3.2	64	-
0.55	0.39 (8)	71	0.79	144	5.6	3.8 (8)	68	4.0	71	-
0.69	0.44 (9)	64	0.77	112	5.1	3.6 (9)	71	4.8	94	-
g/kg neat VX, single drop										

Part 2 of 4

2-60, D.M.H.	W	2[illegible]							38	0.26	36	0.68	0.56
3-60, D.R.T.	W	3[illegible]						0.38 (10)	77	0.50	67	0.78	0.62
4-60, R.F.B.	W	21	81	13.5	12.0	+1.5	0.67	0.59 (10)	88	0.54	80	0.81	0.72
6-60, J.H.H.	W	19	69	9.8	11.2	+1.4	0.79	0.59 (8)	75	0.50	63	0.67	0.49
19-59, J.P.B.	W	21	82	-	-	-	0.99	0.63 (11)	64	0.58	59	1.00	0.63
23-59, L.R.DeL.	W	21	80	-	-	-	0.91	0.39 (8)	43	0.23	25	0.81	0.74
27-59, D.W.	W	20	73	3.7	14.0	+8.68	0.86	0.62 (10)	72	-	-	-	0.52
33-59, G.H.M.	W	21	73	2.2	7.6	+5.4	0.80	0.70 (11)	88	0.74	92	0.51	0.39
34-59, H.E.K.	W	29	93	2.6	5.9	+3.3	0.90	0.65 (8)	72	0.70	78	0.70	0.44
20 µg/kg neat VX,													
29-60, T.A.F.	W	22	80	74.1	77.8	+3.7	0.77	0.50 (10)	65	0.51	66	0.74	0.10
30-60, E.R.R.	W	29	70	93.7	99.4	+5.7	0.80	0.57 (10)	71	0.32	40	0.77	0.60
31-60, J.F.S.	W	21	65	101.7	108.1	+6.4	0.86	0.55 (10)	64	0.39	45	0.67	0.51
32-60, C.J.S.	W	18	60	77.4	81.4	+4.0	0.61	0.11 (10)	18	0.13	21	0.73	0.41
33-60, E.P.B.	W	32	70	84.4	88.9	+4.5	0.84	0.32 (10)	38	0.44	52	0.76	0.67
35-60, E.J.K.	W	18	69	94.2	103.5	-9.3	0.83	0.60 (8)	72	0.51	61	0.66	0.53
36-60, G.F.F.	W	20	76	69.0	68.3	-0.7	0.77	0.20 (10)	26	0.21	27	0.74	0.65
25-60, A.D.DeP.	W	20	75	55.8	67.0	+11.2	0.75	0.66 (5)	88	0.73	97	0.80	0.76
26-60, L.E.K.	W	18	68	59.4	61.1	+1.7	0.78	0.61 (12)	78	0.60	77	0.69	0.64
27-60, F.R.L.	W	20	61	67.2	72.5	+5.3	0.79	0.40 (7)	50	0.43	54	0.53	0.52
28-60, A.B.M.	W	24	96	86.9	88.8	+1.9	0.89	0.74 (8)	83	0.74	86	0.90	0.80
34-60, C.H.C.	N	28	72	86.9	85.6	-1.3	0.76	0.51 (10)	67	0.41	54	0.69	0.58
25 µg/kg neat VX,													
45-59, T.L.A.	W	26	87	1.8	10.6	+8.8	0.82	0.70 (13)	85	0.62	76	0.82	0.42
46-59, S.A.M.	W	20	63	2.5	10.6	8.1	0.83	0.24 (11)	29	0.30	36	0.91	0.52
52-59, B.C.R.	W	19	65	2.7	14.8	12.1	-	- -	-	-	-	-	-
69-59, F.J.W.	W	21	79	3.8	16.0	12.2	0.69	0.63 (9)	91	0.49	71	0.62	0.27
70-59, F.R.L.	W	28	93	2.9	17.4	14.5	0.72	0.71 (9)	99	0.75	104	0.83	0.64
71-59, N.A.F.	W	24	75	3.2	16.2	13.0	0.66	0.35 (9)	53	0.31	47	0.72	0.48
72-59, D.D.	W	30	80	2.3	13.8	11.5	0.71	0.23 -	32	0.20	28	0.71	0.45
30 µg/kg neat VX,													
7-60, S.B.	N	30	74	11.1	11.6	0.5	0.61	0.44 (12)	72	0.36	58	0.73	0.61
8-60, J.S.	W	24	80	15.2	18.7	3.5	0.76	0.62 (10)	82	0.53	70	0.59	0.62
66-59, M.I.C.	W	21	57	3.6	14.0	10.4	0.73	0.56 (8)	77	0.40	55	0.61	0.37
67-59, L.E.B.	W	18	56	3.9	13.5	9.6	0.71	0.45 (8)	63	0.45	63	0.55	0.39
68-59, A.P.H.	W	21	78	3.2	18.9	15.7	0.68	0.60 (9)	88	0.63	93	0.69	0.44
35 µg/kg neat VX,													
17-60, T.E.	W	24	70	14.6	17.6	3.0	0.81	0.12 (10)	15	0.13	16	0.89	0.52
18-60, R.F.	W	21	61	18.2	23.3	5.1	0.85	0.50 (11)	59	0.39	46	0.61	0.57
19-60, B.G.	W	31	70	14.2	21.8	7.6	0.92	0.20 (14)	22	0.19	21	0.84	0.52
20-60, R.G.	W	20	62	14.4	19.6	5.2	0.95	0.48 (11)	50	0.23	24	1.07	0.84
21-60, L.H.	W	26	83	18.9	20.3	1.4	0.84	0.08 (12)	10	0.45	54	0.87	0.37
22-60, W.L.	W	21	83	18.2	14.4	-3.8	0.79	0.52 (10)	66	0.30	38	0.65	0.34
23-60, R.H.S.	W	22	69	12.8	11.7	-1.1	0.71	0.08 (9)	11	0.11	15	0.97	0.36
24-60, L.M.	W	31	77	15.7	19.0	+3.3	0.84	0.19 (11)	23	0.08	10	0.87	0.39

* Figures in parentheses refer to hours after application of agent at which minimum values were reached.

Part 3 of 4

0.68	0.56 (10)	82	0.48	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	-	Nausea; bowel sounds
0.78	0.62 (10)	80	0.63						-	-
0.81	0.72 (10)	89	0.94	116	6.1	3.9 (6)	64	-	-	-
0.67	0.49 (2)	73	0.77	115	7.5	4.4 (6)	59	-	-	-
1.00	0.63 (11)	63	0.64	64	6.3	4.4 (8)	70	3.7	59	-
0.81	0.74 (7)	91	0.71	88	6.7	2.0 (5)	30	3.4	50	Erythema; nausea; fasciculation; pain
-	0.52 (5)	90	-	-	5.2	4.0 (10)	77		-	-
0.51	0.39 (5)	76	0.63	123	4.4	4.4 (5)	100	4.7	106	-
0.70	0.44 (4)	63	0.83	120	6.2	5.0 (10)	81	4.9	79	-
20 μg/kg neat VX, five drops										
0.74	0.10 (10)	13	0.80	108	-	-	-	-	-	-
0.77	0.60 (10)	78	0.74	96	-	-	-	-	-	-
0.67	0.51 (10)	76	0.66	99	-	-	-	-	-	-
0.73	0.41 (10)	56	0.44	60	4.7	-	-	-	-	Nausea; vomiting; administered 2 mg of atropine
0.76	0.67 (10)	88	0.78	103	-	-	-	-	-	-
0.66	0.53 (10)	80	0.73	111	-	-	-	-	-	-
0.74	0.65 (8)	88	0.70	95	-	-	-	-	-	-
0.80	0.76 (5)	95	0.80	100	5.0	-	-	-	-	-
0.69	0.64 (2)	93	0.96	139	5.0	-	-	-	-	-
0.53	0.52 -	98	0.59	111	4.8	-	-	-	-	-
0.90	0.80 (8)	89	1.12	124	5.2	-	-	-	-	-
0.69	0.58 (10)	84	0.77	112		-	-	-	-	-
25 μg/kg neat VX, single drop										
0.82	0.42 (8)	51	0.54	66	5.6	5.1 (5)	91	5.6	100	Fasciculation; nausea; vomiting; headache
0.91	0.52 (8)	57	0.50	55	5.6	1.4 (12)	25	1.6	28	-
-	- -	-	-	-	6.3	1.7 (11)	27	1.2	19	-
0.62	0.27 (8)	44	0.58	94	5.7	4.7 (9)	83	4.8	84	-
0.83	0.64 (2)	77	0.95	114	6.3	5.1 (8)	81	5.1	81	-
0.72	0.48 (9)	67	0.57	79	5.3	2.5 (8)	47	2.4	45	-
0.71	0.45 (6)	63	0.41	58	6.3	1.1 (8)	17	1.7	27	Headache; bowel sounds
30 μg/kg neat VX, single drop										
0.73	0.61 (10)	84	0.80	110	6.3	4.0 (10)	63	-	-	-
0.59	0.62 (10)	105	0.79	134	7.3	5.8 (7)	79	-	-	-
0.61	0.37 (8)	61	0.53	87	5.0	3.5 (9)	70	3.2	64	-
0.55	0.39 (8)	71	0.79	144	5.6	3.8 (8)	68	4.0	71	-
0.69	0.44 (9)	64	0.77	112	5.1	3.6 (9)	71	4.8	94	-
35 μg/kg neat VX, single drop										
0.89	0.52 (8)	58	0.47	53	5.5	1.2 (10)	22	1.4	25	Vomiting; nausea; administered 2 mg of atropine
0.61	0.57 (8)	93	0.66	108	6.2	4.8 (4)	77	4.2	68	-
0.84	0.52 (8)	62	0.59	70	6.2	2.4 (10)	39	2.6	42	-
1.07	0.84 (8)	78	0.85	79	6.5	4.6 (10)	71	3.7	57	-
0.87	0.37 (12)	43	0.52	60	6.1	1.0 (11)	16	3.2	52	Vomiting; nausea; administered 1 g oral of P_2 and 6 mg of atropine
0.65	0.34 (11)	52	0.37	57	5.8	4.0 (8)	69	3.2	55	-
0.97	0.36 (11)	37	0.51	53	5.5	0.5 (8)	9	1.6	29	Vomiting; nausea; administered 6 mg of atropine, 1 g oral of P_2S, and 0.5 g im of P_2S
0.87	0.39 (10)	45	0.50	57	6.1	1.4 (11)	23	1.2	20	Vomiting; nausea; administered 5 mg of atropine, 1 g oral of P_2S, and 15 mg im of Pro-Banthine Bromide

Part 4 of 4 UNCLASSIFIED

(C) ~~CONFIDENTIAL~~ Part 1 of 4

TABLE 2

EFFECT OF SINGLE DROP OF VX WITH AMI

Subject	Race	Age	Weight	Spread			RBC				Plasm		
				Early	Late	Maximum	Initial	Minimal*		At 24 hr	Initial	Minimal*	
			kg	sq cm			ΔpH		% initial	ΔpH % initial	ΔpH		% init
10 μg/kg n-octylamine plus 10 μg/kg VX													
20-59, T.J.B.	W	34	67	-	-	-	0.97	0.83 (11)	86	0.81 84	0.77	0.63 (6)	8
10 μg/kg n-decylamine plus 10 μg/kg VX													
21-59, G	W	24	52	-	-	-	0.83	0.66 (10)	80	0.63 76	0.67	0.49 (3)	7
10 μg/kg di-n-hexylamine plus 10 μg/kg V													
22-59, H.J.	W	25	72	-	-	-	0.95	0.79 (8)	83	0.71 75	0.73	0.57 (6)	7
15 μg/kg n-octylamine plus 15 μg/kg VX													
35-59, J.H.P.	W	24	78	2.4	5.7	3.3	0.78	0.72 (8)	92	0.73 94	0.59	0.48 (5)	8
24-59, L.D.M.	N	19	70	3.3	6.4	3.1	0.79	0.51 (6)	65	0.81 103	0.80	0.67 (9)	8
28-59, I.O.H.	N	31	63	3.0	15.8	12.8	0.96	0.90 (3)	94	- -	0.60	0.63 (4)	10
15 μg/kg n-decylamine plus 15 μg/kg VX													
25-59, D.J.P.	W	23	80	2.2	8.0	5.8	0.81	0.54 (9)	67	0.62 77	1.20	1.09 (7)	9
29-59, M.D.R.	W	19	70	3.7	13.5	9.8	0.82	0.59 (10)	72	- -	0.86	0.71 (6)	8
32-59, C.E.A.	W	34	89	1.0	2.2	1.2	0.84	0.39 (11)	46	0.46 55	0.78	0.44 (5)	5
38-59, R.N.	W	25	88	1.7	3.5	1.28	0.79	0.51 (8)	65	0.52 66	0.77	0.58 (6)	7
42-59, P.G.M.	[illegible]	21	74	2.0	3.6	1.6	0.78	0.26 (8)	33	0.26 33	0.77	0.69 (6)	9
64-59, C.A.F.	[illegible]	30	87	4.6	4.4	-0.2	0.75	0.51 (12)	68	0.62 83	0.68	0.54 (12)	7
65-59, J.J.F.	W	24	90	5.9	3.0	-2.9	0.73	0.12 (12)	16	0.24 33	0.75	0.37 (10)	4
60-59, L.E.O.	W	28	86	3.5	4.8	1.3	0.91	0.54 (12)	59	0.53 58	0.82	0.53 (12)	6
61-59, H.A.D.	W	22	77	5.5	3.5	2.0	0.80	0.11 (12)	14	0.17 21	0.60	0.29 (12)	4
41-59, R.C.K.	W	19	85	2.3	19.4	17.1	0.81	0.65 (4)	80	0.60 74	0.59	0.62 -	10
15 μg/kg n-dodecylamine plus 15 μg/kg VX													
39-59, D.M.N.	W	21	68	1.0	3.0	2.0	0.83	0.66 (4)	80	0.61 73	0.69	0.53 (3)	7
40-59, J.A.S.	W	33	93	0.8	4.8	4.0	0.83	0.73 (4)	88	0.71 85	0.93	0.69 (3)	7
43-59, R.H.M.	W	24	75	0.5	4.1	3.6	0.71	0.52 (4)	73	0.52 73	0.61	0.75 (4)	12
44-59, C.A.U.	W	20	77	0.7	4.6	3.9	0.71	0.38 (10)	54	0.42 59	0.73	0.73 (6)	10
74-59, F.C.O.	W	29	66	0.8	4.8	4.0	0.69	0.29 (10)	42	0.24 35	0.60	0.61 (8)	10
73-59, L.B.	N	24	65	0.4	4.4	4.0	0.66	0.44 (10)	67	0.34 52	0.59	0.50 (8)	8
15 μg/kg di-n-hexylamine plus 15 μg/kg V													
26-59, R.R.	W	20	62	5.5	7.8	2.3	0.90	0.71 (8)	79	0.81 90	0.89	0.80 (1)	9
30-59, H.W.Z.	W	31	89	5.6	20.7	15.1	0.93	0.79 (11)	85	- -	0.61	0.65 (5)	10
36-59, W.B.D.	W	20	65	4.9	9.9	5.0	0.76	0.72 (10)	95	0.73 96	0.78	0.61 (4)	7
20 μg/kg n-octylamine plus 20 μg/kg VX													
9-60, O.E.A.	W	35	103	11.70	15.18	+3.5	0.83	0.40 (12)	48	0.38 46	0.92	0.60 (8)	6
10-60, R.D.B.	W	22	79	7.60	8.4	+0.8	0.74	0.16 (12)	21	0.27 36	0.88	0.39 (12)	4
11-60, J.T.B.	N	42	75	7.26	7.35	0.09	0.91	0.38 (12)	42	0.49 54	0.61	0.48 (12)	7
12-60, D.E.B.	W	24	61	-	-	-	0.80	0.20 (12)	25	0.36 45	0.69	0.28 (12)	4
13-60, J.F.T.	W	21	86	10.5	11.34	+0.8	0.80	0.21 (12)	26	0.37 46	0.72	0.50 (10)	6
14-60, R.L.C.	W	24	79	-	-	-	0.90	0.10 (12)	11	0.33 37	0.68	0.38 (12)	5
15-60, C.L.C	W	24	58	-	-	-	0.75	0.11 (12)	15	0.33 44	0.87	0.42 (12)	4
16-60, R.M.D.	W	30	85	-	-	-	0.82	0.15 (10)	18	0.44 54	0.93	0.52 (12)	5
20 μg/kg n-decylamine plus 20 μg/kg VX													
47-59, G.E.C.	W	34	82	5.70	10.24	+4.5	0.75	0.22 (10)	29	0.23 31	0.99	0.54 (10)	5
48-59, J.G.S.	W	33	66	5.70	10.24	+4.5	0.75	0.22 (10)	29	0.23 31	0.99	0.54 (10)	5

TABLE 2

P OF VX WITH AMINES ON MAN (C)

Cholinesterase								Local and systemic signs and symptoms
Plasma				Whole blood				
Minimal*		At 24 hr		Initial	Minimal*		At 24 hr	
ΔpH	% initial	ΔpH	% initial	μeq/ml min^{-1}	% initial	μeq/ml min^{-1}	% initial	
lus 10 μg/kg VX plus 1% Hiltamine								
0.63 (6)	82	0.62	81	6.2	5.2 (10)	84	4.9	79	-
lus 10 μg/kg VX plus 1% Hiltamine								
0.49 (3)	73	0.55	82	6.1	4.6 (10)	75	4.3	71	-
e plus 10 μg/kg VX plus 1% Hiltamine								
0.57 (6)	78	0.69	95	6.3	5.7(10)	90	5.4	86	-
lus 15 μg/kg VX plus 1% Hiltamine								
0.48 (5)	81	0.75	127	5.5	4.7 (10)	86	4.7	86	-
0.67 (9)	84	0.77	97	6.7	5.8 (8)	87	6.5	97	Erythema (control arm)
0.63 (4)	105	-	-	5.8	5.8 (2)	100	-	-	Hiltamine visual flow along superficial vein on volar surface of upper arm to approx 10 in. from original site of application
lus 15 μg/kg VX plus 1% Hiltamine								
1.09 (7)	91	1.08	90	6.0	5.0 (9)	83	5.5	92	Erythema (control arm)
0.71 (6)	83	-	-	5.8	3.6 (10)	62	-	-	-
0.44 (5)	56	0.45	58	5.3	2.2 (6)	42	2.5	49	-
0.58 (6)	75	0.59	77	5.0	3.0 (6)	60	5.0	100	-
0.69 (6)	90	0.80	104	5.7	1.6 (10)	28	2.7	47	-
0.54 (12)	79	0.76	112	5.7	4.6 (11)	81	4.7	83	-
0.37 (10)	49	0.58	77	6.0	1.0 (12)	17	-	-	-
0.53 (12)	65	0.78	95	6.3	3.6 (12)	57	3.1	49	-
0.29 (12)	48	0.34	57	5.3	0.9 (10)	17	-	-	Nausea; vomiting; extremely weakened; administered 2 mg of atropine
0.62 -	105	0.78	132	5.7	4.3 (6)	75	5.0	88	Burn in 1 hr; small blister in 1-1/2 hr
plus 15 μg/kg VX plus 1% Hiltamine								
0.53 (3)	77	0.62	90	4.8	3.9 (8)	81	4.7	98	Erythema; small blister
0.69 (3)	74	0.89	96	5.4	4.8 (3)	89	5.4	100	-
0.75 (4)	123	0.96	157	5.3	4.7 (6)	89	4.7	89	-
0.73 (6)	100	0.80	109	5.2	3.0 (6)	58	3.4	65	-
0.61 (8)	102	0.52	87	5.3	1.9 (10)	36	1.9	36	-
0.50 (8)	85	0.52	88	5.1	2.9 (11)	57	2.0	39	Nausea; vomiting
e plus 15 μg/kg VX plus 1% Hiltamine								
0.80 (1)	90	1.27	143	6.9	5.8 (9)	84	7.0	101	Erythema
0.65 (5)	106	-	-	6.1	4.9 (10)	80	-	-	-
0.61 (4)	78	0.92	118	5.5	5.1 (6)	93	5.2	95	-
lus 20 μg/kg VX plus 1% Hiltamine								
0.60 (8)	65	0.67	73	6.7	2.9 (12)	43	2.0	30	Mild diarrhea; vomiting
0.39 (12)	44	0.59	67	6.3	1.0 (12)	16	1.5	24	Vomiting; nausea
0.48 (12)	79	0.64	105	6.6	2.8 (10)	42	3.2	48	Nausea at 6 hr
0.28 (12)	41	0.58	84	5.8	0.8 (12)	14	1.6	28	Vomiting at 6 hr; nausea at 6 hr
0.50 (10)	69	0.67	93	6.0	1.2 (12)	20	1.9	32	Tightness of chest
0.38 (12)	56	0.58	85	5.6	0.6 (10)	11	1.4	25	Administered 3 mg im of atropine
0.42 (12)	48	0.58	67	5.6	0.9 (12)	16	1.1	20	Nausea at 8 hr
0.52 (12)	56	0.66	71	5.8	0.5 (9)	9	2.0	34	Administered 3 mg im of atropine
lus 20 μg/kg VX plus 1% Hiltamine								
0.54 (10)	55	0.56	56	5.2	1.3 (12)	25	1.8	35	Sick at 7 hr
0.54 (10)	55	0.56	56	6.3	1.5 (10)	24	2.0	32	Erythema; fasciculation; nausea; vomiting

Part 2 of 4

25-59, D.J.P.	W	23	80							0.62	77	1.20	1.09 (7)	
29-59, M.D.R.	W	19	70							-	-	0.86	0.71 (6)	
32-59, C.E.A.	W	34	89	1.0	2.2	1.2	0.84	0.39 (11)	46	0.46	55	0.78	0.44 (5)	
38-59, R.N.	W	25	88	1.7	3.5	1.28	0.79	0.51 (8)	65	0.52	66	0.77	0.58 (6)	
42-59, P.G.M.	W	21	74	2.0	3.6	1.6	0.78	0.26 (8)	33	0.26	33	0.77	0.69 (6)	
64-59, C.A.F.	W	30	87	4.6	4.4	-0.2	0.75	0.51 (12)	68	0.62	83	0.68	0.54 (12)	
65-59, J.J.F.	W	24	90	5.9	3.0	-2.9	0.73	0.12 (12)	16	0.24	33	0.75	0.37 (10)	
60-59, L.E.O.	W	28	86	3.5	4.8	1.3	0.91	0.54 (12)	59	0.53	58	0.82	0.53 (12)	
61-59, H.A.D.	W	22	77	5.5	3.5	2.0	0.80	0.11 (12)	14	0.17	21	0.60	0.29 (12)	
41-59, R.C.K.	W	19	85	2.3	19.4	17.1	0.81	0.65 (4)	80	0.60	74	0.59	0.62 -	
15 μg/kg n-dodecylamine plus 15 μg/kg VX														
39-59, D.M.N.	W	21	68	1.0	3.0	2.0	0.83	0.66 (4)	80	0.61	73	0.69	0.53 (3)	
40-59, J.A.S.	W	33	93	0.8	4.8	4.0	0.83	0.73 (4)	88	0.71	85	0.93	0.69 (3)	
43-59, R.H.M.	W	24	75	0.5	4.1	3.6	0.71	0.52 (4)	73	0.52	73	0.61	0.75 (4)	
44-59, C.A.U.	W	20	77	0.7	4.6	3.9	0.71	0.38 (10)	54	0.42	59	0.73	0.73 (6)	
74-59, F.C.O.	W	29	66	0.8	4.8	4.0	0.69	0.29 (10)	42	0.24	35	0.60	0.61 (8)	
73-59, L.B.	N	24	65	0.4	4.4	4.0	0.66	0.44 (10)	67	0.34	52	0.59	0.50 (8)	
15 μg/kg di-n-hexylamine plus 15 μg/kg														
26-59, R.R.	W	20	62	5.5	7.8	2.3	0.90	0.71 (8)	79	0.81	90	0.89	0.80 (1)	
30-59, H.W.Z.	W	31	89	5.6	20.7	15.1	0.93	0.79 (11)	85	-	-	0.61	0.65 (5)	
36-59, W.B.D.	W	20	65	4.9	9.9	5.0	0.76	0.72 (10)	95	0.73	96	0.78	0.61 (4)	
20 μg/kg n-octylamine plus 20 μg/kg VX														
9-60, O.E.A.	W	35	103	11.70	15.18	+3.5	0.83	0.40 (12)	48	0.38	46	0.92	0.60 (8)	
10-60, R.D.B.	W	22	79	7.60	8.4	+0.8	0.74	0.16 (12)	21	0.27	36	0.88	0.39 (12)	
11-60, J.T.B.	N	42	75	7.26	7.35	0.09	0.91	0.38 (12)	42	0.49	54	0.61	0.48 (12)	
12-60, D.E.B.	W	24	61	-	-	-	0.80	0.20 (12)	25	0.36	45	0.69	0.28 (12)	
13-60, J.F.T.	W	21	86	10.5	11.34	+0.8	0.80	0.21 (12)	26	0.37	46	0.72	0.50 (10)	
14-60, R.L.C.	W	24	79	-	-	-	0.90	0.10 (12)	11	0.33	37	0.68	0.38 (12)	
15-60, C.L.C	W	24	58	-	-	-	0.75	0.11 (12)	15	0.33	44	0.87	0.42 (12)	
16-60, R.M.D.	W	30	85	-	-	-	0.82	0.15 (10)	18	0.44	54	0.93	0.52 (12)	
20 μg/kg n-decylamine plus 20 μg/kg VX														
47-59, G.E.C.	W	34	82	5.70	10.24	+4.5	0.75	0.22 (10)	29	0.23	31	0.99	0.54 (10)	
48-59, J.G.S.	W	33	66	5.70	10.24	+4.5	0.75	0.22 (10)	29	0.23	31	0.99	0.54 (10)	
54-59, L.E.M.	W	19	82	3.75	7.04	+4.0	0.84	0.35 (11)	42	0.32	38	0.68	0.33 (11)	
55-59, B.B.	W	28	95	5.75	7.56	+2.0	-	-	-	-	-	-	--	
56-59, W.H.	N	30	73	3.64	4.64	+1.0	0.72	0.35 (12)	49	0.32	44	0.60	0.30 (4)	
57-59, E.G.H.	W	19	80	6.0	7.29	+1.3	0.70	0.18 (12)	26	0.29	41	0.77	0.50 (12)	
58-59, T.G.N.	W	20	76	-	-	-	0.78	0.22 (12)	28	0.39	50	0.59	0.41 (12)	
59-59, J.R.N.	W	27	80	4.5	7.8	+3.3	0.75	0.40 (12)	53	0.36	48	0.56	0.43 (12)	
62-59, O.W.S.	W	24	65	3.4	4.3	+0.8	0.71	0.12 (10)	17	0.12	17	0.66	0.28 (10)	
63-59, P.J.L.	W	20	87	5.5	9.6	+4.1	0.78	0.25 (12)	32	0.38	49	0.91	0.48 (12)	
20 μg/kg n-dodecylamine plus 20 μg/kg VX														
49-59, F.B.P.	W	34	72	2.3	3.08	+0.78	0.78	0.73 (12)	94	0.62	79	1.03	0.79 (6)	
50-59, R.G.K.	W	21	90	3.3	4.7	+1.4	0.78	0.27 (11)	35	0.29	37	0.82	0.61 (11)	
75-59, D.A.	W	25	58	4.0	6.0	+2.0	0.69	0.29 (10)	42	0.23	33	0.70	0.45 (10)	
76-59, L.R.B.	W	24	84	5.9	9.0	+3.01	0.81	0.58 (10)	72	0.36	44	0.70	0.44 (8)	
77-59, J.D.	W	20	76	3.8	8.0	+4.2	0.61	0.25 (12	41	0.15	25	0.68	0.54 (10)	
78-59, L.M.F.	W	21	75	7.5	9.2	+1.7	0.75	0.40 (12)	53	0.37	49	0.49	1.00 -	
79-59, E.C.K.	W	23	80	3.6	5.2	+1.6	0.63	0.20 (12)	32	0.17	27	0.48	0.38 (4)	
80-59, R.H.M.	N	27	75	1.6	4.3	+2.7	0.65	0.63 (9)	97	0.57	88	0.45	0.39 (9)	

* Figures in parentheses refer to hours after application of agent at which minimum values were reached

)9 (7)	91	1.08	90	6.0	**5.0 (9)**	**83**	**5.5**	92	Erythema (control arm)
'1 (6)	83	-	-	5.8	3.6 (10)	62	-	-	-
;4 (5)	56	0.45	58	5.3	2.2 (6)	42	2.5	49	-
;8 (6)	75	0.59	77	5.0	3.0 (6)	60	5.0	100	-
;9 (6)	90	0.80	104	5.7	1.6 (10)	28	2.7	47	-
;4 (12)	79	0.76	112	5.7	4.6 (11)	81	4.7	83	-
)7 (10)	49	0.58	77	6.0	1.0 (12)	17	-	-	-
;3 (12)	65	0.78	95	6.3	3.6 (12)	57	3.1	49	-
;9 (12)	48	0.34	57	5.3	0.9 (10)	17	-	-	Nausea; vomiting; extremely weakened; administered 2 mg of atropine
;2 -	105	0.78	132	5.7	4.3 (6)	75	5.0	88	Burn in 1 hr; small blister in 1-1/2 hr
ıs 15 μg/kg VX plus 1% Hiltamine									
;3 (3)	77	0.62	90	4.8	3.9 (8)	81	4.7	98	Erythema; small blister
;9 (3)	74	0.89	96	5.4	4.8 (3)	89	5.4	100	-
;5 (4)	123	0.96	157	5.3	4.7 (6)	89	4.7	89	-
;3 (6)	100	0.80	109	5.2	3.0 (6)	58	3.4	65	-
;1 (8)	102	0.52	87	5.3	1.9 (10)	36	1.9	36	-
;0 (8)	85	0.52	88	5.1	2.9 (11)	57	2.0	39	Nausea; vomiting
lus 15 μg/kg VX plus 1% Hiltamine									
;0 (1)	90	1.27	143	6.9	5.8 (9)	84	7.0	101	Erythema
;5 (5)	106	-	-	6.1	4.9 (10)	80	-	-	-
;1 (4)	78	0.92	118	5.5	5.1 (6)	93	5.2	95	-
20 μg/kg VX plus 1% Hiltamine									
;0 (8)	65	0.67	73	6.7	2.9 (12)	43	2.0	30	Mild diarrhea; vomiting
;9 (12)	44	0.59	67	6.3	1.0 (12)	16	1.5	24	Vomiting; nausea
;8 (12)	79	0.64	105	6.6	2.8 (10)	42	3.2	48	Nausea at 6 hr
;8 (12)	41	0.58	84	5.8	0.8 (12)	14	1.6	28	Vomiting at 6 hr; nausea at 6 hr
;0 (10)	69	0.67	93	6.0	1.2 (12)	20	1.9	32	Tightness of chest
;8 (12)	56	0.58	85	5.6	0.6 (10)	11	1.4	25	Administered 3 mg im of atropine
;2 (12)	48	0.58	67	5.6	0.9 (12)	16	1.1	20	Nausea at 8 hr
;2 (12)	56	0.66	71	5.8	0.5 (9)	9	2.0	34	Administered 3 mg im of atropine
20 μg/kg VX plus 1% Hiltamine									
;4 (10)	55	0.56	56	5.2	1.3 (12)	25	1.8	35	Sick at 7 hr
;4 (10)	55	0.56	56	6.3	1.5 (10)	24	2.0	32	Erythema; fasciculation; nausea; vomiting
;3 (11)	49	0.31	46	5.3	1.2 (11)	23	1.7	32	-
	-	-	-	5.3	2.1 (10)	40	2.5	47	-
;0 (4)	50	0.51	85	5.0	2.6 (12)	52	-	-	-
;0 (12)	65	0.30	39	4.9	1.5 (12)	31	-	-	Nausea; vomiting; weakness; sick at 7 hr
;1 (12)	69	0.68	115	5.1	2.2 (12)	43	-	-	-
;3 (12)	77	0.38	68	5.2	2.4 (12)	46	1.9	37	-
;8 (10)	42	0.34	52	4.8	0.9 (12)	19	0.9	19	Abdominal pain; nausea; vomiting; sick at 9 hr
;8 (12)	53	0.80	88	5.0	2.6 (12)	52	-	-	-
us 20 μg/kg VX plus 1% Hiltamine									
;9 (6)	77	0.87	84	6.6	5.5 (4)	83	-	-	-
;1 (11)	70	0.63	77	5.3	2.0 (10)	38	-	-	-
;5 (10)	64	0.64	91	4.8	-	-	1.9	40	Nausea; vomiting; sick at 11 hr
;4 (8)	63	0.61	87	6.3	-	-	3.0	48	Nausea; vomiting
;4 (10)	79	0.50	74	5.2	-	-	1.2	23	Sick
00 -	100	0.48	98	6.3	-	-	3.0	48	-
;8 (4)	79	0.41	85	4.5	0.7 (11)	16	1.1	24	Nausea; vomiting; administered 12 mg of atropine
;9 (9)	87	0.48	107	5.0	-	-	3.7	74	-

Part 4 of 4

AD_____ Accession No. _____
Clinical Research Division, U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland
VX PERCUTANEOUS STUDIES IN MAN (U) - Van M. Sim, M. D., and Jane L. Stubbs

CRDLR 3015, August 1960
Project 4C08-02-022, CONFIDENTIAL REPORT

(C) The effect of percutaneous administration of VX to 103 subjects using 50, 100, 200 μ aerosol particles, single and multiple drops, was studied. VX as neat agent, in doses from 5 to 35 μg/kg, and VX combined in a 1:1 mixture with each of n-octylamine, n-decylamine, or n-dodecylamine, in doses from 10 to 20 μg/kg, were used. The site of application used was the right volar forearm. Both neat and agent-amine mixtures decreased the electrical resistance of the skin. One-to-one mixtures of n-octylamine or n-decylamine with 20 μg/kg of VX were about as effective as 35 μg/kg of neat agent. Twenty-five of the 68 subjects who received either neat agent in doses of 20 to 35 μg/kg or amine-agent mixtures containing doses of 20 μg/kg of VX developed clinical signs and symptoms of anticholinesterase poisoning.

1. VX, percut studies in man
2. n-Octylamine Mixture, percut studies in man, VX-
3. n-Decylamine Mixture, percut studies in man, VX-
4. n-Dodecylamine Mixture, percut studies in man, VX-

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DEPARTMENT OF THE ARMY
US ARMY RESEARCH, DEVELOPMENT AND ENGINEERING COMMAND
EDGEWOOD CHEMICAL BIOLOGICAL CENTER
5183 BLACKHAWK ROAD
ABERDEEN PROVING GROUND, MD 21010-5424

REPLY TO
ATTENTION OF

JAN 06 2017

RDCB-DSR-S

MEMORANDUM THRU Director, Edgewood Chemical Biological Center, (RDCB-D/Dr. Joseph L. Corriveau), 5183 Blackhawk Road, Aberdeen Proving Ground, Maryland 21010-5424

FOR Defense Technical Information Center (DTIC), 8725 John J. Kingman Road, Ft Belvoir, VA 22060-6218

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1. This action is in response to an Edgewood Chemical Biological Center (ECBC) Internal Request for a Change in Distribution for the attached listed documents:

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3. The point of contact is Adana Eilo, ECBC Security Specialist, (410) 436-2063 or adana.l.eilo.civ@mail.mil.

Encl

RONALD L. STAFFORD
Security Manager

ECBC Documents for Downgrading/Change in Distribution

1. Callahan, J.F. *The Relation between Skin Thickness and the Penetration Rate of VX through Skin.* In *Research Program of the Field Toxicology Branch;* CRDL TM 20-27; Callahan, JF, *et al.* Eds.; Directorate of Medical Research, U.S. Army Chemical Research and Development Laboratories, U.S. Army Chemical Center: Edgewood Arsenal, MD, 1962; UNCLASSIFIED Report. **CBRNIAC-CB-118810 Dist. E.**
Recommended for public release.

2. Callahan, J.F.; Cresthull, P.; Christensen, M.K.; Crook, J.W.; Wiles J.S.; Owens, E.; Hart, J.; Worden, F.X. *Intravenous Toxicity of VX* in Marzulli *et al. Biological Studies on VX during Fiscal Year 1958*; CWL Special Publication 2-18; U.S. Army Chemical Warfare Laboratories: U.S. Army Chemical Center, 1959; UNCLASSIFIED Report **AD0313760 Dist. C.**
Recommended for public release.

3. Frankel, H.M.; Wiles, J.S. *Lethality of VX in Rats at High and Low Temperatures;* CRDLR-3023; U.S. Army Chemical Research, and Development Laboratories: Edgewood Arsenal, MD, 1960; UNCLASSIFIED Report **AD0243462 Dist C.**
Recommended for public release.

4. Marzulli, F.N. *A Comparison of Toxic Properties of the V Agents with GB*; MLSR-75; U.S. Army Chemical Corp Medical Laboratories: U.S. Army Chemical Center, MD, 1955; UNCLASSIFIED Report **AD0090916 Dist. C.**
Recommended for public release.

5. Reutter-Christy, S.A.; Sommerville, D.R.; Edward M. Jakubowski; Christopher E. Whalley; Bernard J. Benton; Stanley W. Hulet; Paul A. Dabisch; Ronald A. Evans; Jeffrey M. McGuire; Charles L. Crouse; R Christopher E. Byers; James H. Manthei; Ruth W. Moretz; Jeffry S. Forster; Bernardita I. Gaviola; David C. Burnett; William T. Muse; Kathy L. Matson; Robert J. Mioduszewski; Sandra A. Thomson; Julie A. Renner; Allison L. Totura; Edward J. Emm; Stephen R. Channel; Tsung-Ming Shih; Lucille A. Lumley; John O'Donnell; Theresa Ward; Bountieng Somsamayvong; Christopher Robison; Susan Schulz; Kelly L. Ault; Edward D. Clarkson; Raymond F. Genovese; John L. Oubre; Patrick J. Fleming. *Chemical Warfare Agent Operational Exposure Hazard Assessment Research: FY07 Report and Analysis*; ECBC-TR-784; U.S. Army Edgewood Chemical Biological Center: Aberdeen Proving Ground, MD, 2010a.
ADB370363 Dist. C. Recommended for public release.

6. Reutter, Sharon A.; Moretz, Ruth W.; Murray, Michele M.; Sommerville, Douglas R., *Review of Toxicological Data Regarding Contact Hazards of Chemical Agents*, ECBC-TR-514; U.S. Army Edgewood Chemical Biological Center: Aberdeen Proving Ground, MD, 2006; UNCLASSIFIED Report **ADB321921 Dist. C. Recommended for public release.**

7. Sim, V.M. *Variability of Different Intact Human-Skin Sites to the Penetration of VX*; CRDLR-3122; Chemical Research and Development Laboratories: Edgewood Arsenal, MD, 1962
AD0271163 Dist. C. Export Control Recommended for public release.

8. Sim, V.M; Stubbs, J.E. *VX Percutaneous Studies in Man*; CRDLR-3015; Chemical Research and Development Laboratories: Aberdeen Proving Ground, MD, 1960
AD0318533 Dist. F. Recommended for public release.